



Docket No.: PF-0339-2 CPA

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bandman et al.

Title: NEW HUMAN INTEGRAL MEMBRANE PROTEIN

Serial No.: 09/265,710

Filing Date: March 9, 1999

Examiner: Ulm, J.

Group Art Unit: 1646

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LARS MICHAEL FURNESS
UNDER 37 C.F.R. § 1.132

I, L. MICHAEL FURNESS, a citizen of the United Kingdom, residing at 2 Brookside, Exning, Newmarket, United Kingdom, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Pharmacogenomics until December 31, 2001. I am currently under contract to be a Consultant to Incyte.

2. In 1984, I received a B.Sc.(Hons) in Biomolecular Science (Biophysics and Biochemistry) from Portsmouth Polytechnic.

From 1985-1987 I was at the School of Pharmacy in London, United Kingdom, during which time I analyzed lipid methyltransferase enzymes using a variety of protein analysis methods, including one-dimensional (1D) and two-dimensional (2D) gel electrophoresis, HPLC, and a variety of enzymatic

assay systems.

I then worked in the Protein Structure group at the National Institute for Medical Research until 1989, setting up core facilities for nucleic acid synthesis and sequencing, as well as assisting in programs on protein kinase C inhibitors.

After a year at Perkin Elmer-Applied Biosystems as a technical specialist, I worked at the Imperial Cancer Research Fund between 1990-1992, on a Eureka-funded program collaborating with Amersham Pharmacia in the United Kingdom and CEPH (Centre d'Etude du Polymorphisme Humaine) in Paris, France, to develop novel nucleic acid purification and characterization methods.

In 1992, I moved to Pfizer Central Research in the United Kingdom, where I stayed until 1998, initially setting up core DNA sequencing and then a DNA arraying facility for gene expression analysis in 1993. My work also included bioinformatics and I was responsible for the support of all Pfizer neuroscience programs in the United Kingdom. This then led me into carrying out detailed bioinformatics and wet lab work on the sodium channels, including antibody generation, Western and Northern analyses, PCR, tissue distribution studies, and sequence analyses on novel sequences identified.

In 1998, I moved to Incyte to work in the Pharmacogenomics group, looking at the application of genomics and proteomics to the pharmaceutical industry. In 1999, I was appointed Director of the LifeExpress Lead Program which used microarray and protein expression data to identify pharmacologically and toxicologically relevant mechanisms to assist in improved drug design and development.

On December 12, 2001, I founded Nuomics Consulting, Ltd., in Exning, UK, where I am currently employed as Managing Director. Nuomics Consulting, Ltd. provides expert technical knowledge and advice to businesses in the areas of genomics, proteomics, pharmacogenomics, toxicogenomics, and chemogenomics.

3. I have reviewed the specification of a United States patent application that I understand was filed on March 9, 1999 in the names of Olga Bandman et al. and was assigned Serial No. 09/265,710 (hereinafter "the Bandman '710 application"). Furthermore, I understand that this United States patent

application was a divisional application of, and claimed priority to, United States patent application Serial No. 08/892,690, filed on July 14, 1997 (hereinafter "the Bandman '690 application"), having the identical specification. My remarks herein will therefore be directed to the Bandman '690 patent application, and July 14, 1997, as the relevant date of filing. In broad overview, the Bandman '690 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene and protein expression monitoring applications that are useful in connection with (a) developing drugs (e.g., for the treatment of cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Bandman '710 application contains claims that are directed to an isolated polypeptide having the sequence shown as SEQ ID NO:1 (hereinafter "the SEQ ID NO:1 polypeptide"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Bandman '710 application does not disclose a credible, substantial, and specific asserted utility or a well established utility for the claimed SEQ ID NO:1 polypeptide. I further understand that whether or not a patent specification discloses a credible, substantial, and specific asserted utility or a well established utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time the patent application was filed. In addition, I understand that a credible, substantial, and specific asserted utility or a well established utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Bandman '710 application and its parent, the Bandman '690 application, do not disclose a credible, substantial, and specific "real-world" utility for the claimed SEQ ID NO:1 polypeptide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Bandman '690 application pertains on July 14, 1997, would have concluded that the Bandman '690 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1 polypeptide in its then available and disclosed

form. I have also been informed that, with respect to the “real-world” utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107 of the Manual of Patent Examining Procedure, under the heading “I. ‘Real-World Value’ Requirement”:

“Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact ‘useful’ in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.”

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Bandman ‘690 patent application disclosed to a person skilled in the art at the time of its filing a number of substantial, specific, and credible real-world utilities for the claimed SEQ ID NO:1 polypeptide. More specifically, persons skilled in the art on July 14, 1997, would have understood the Bandman ‘690 application to disclose the use of the SEQ ID NO:1 polypeptide as a research tool in a number of gene and protein expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-13 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Bandman ‘690 application, and (b) a number of published articles and patent documents that evidence gene and protein expression monitoring techniques that were well-known before the July 14, 1997 filing date of the Bandman ‘690 application. The published articles and patent documents I considered are:

(a) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Anderson, N.G., A Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effects Studies, Electrophoresis, 12, 907-930 (1991) (hereinafter “the Anderson 1991 article”) (copy annexed at Tab

A);

(b) Anderson, N.L., Esquer-Blasco, R., Hofmann, J.-P., Mehues, L., Raymackers, J., Steiner, S., Witzmann, F., Anderson, N.G., An Updated Two-Dimensional Gel Database of Rat Liver Proteins Useful in Gene Regulation and Drug Effect Studies, Electrophoresis, 16, 1977-1991 (1995) (hereinafter "the Anderson 1995 article") (copy annexed at Tab B);

(c) Wilkins, M.R., Sanchez, J.-C., Gooley, A.A., Appel, R.D., Humphrey-Smith, I., Hochstrasser, D.F., Williams, K.L., Progress with Proteome Projects: Why all Proteins Expressed by a Genome Should be Identified and How To Do It, Biotechnology and Genetic Engineering Reviews, 13, 19-50 (1995) (hereinafter "the Wilkins article") (copy annexed at Tab C);

(d) Celis, J.E., Rasmussen, H.H., Leffers, H., Madsen, P., Honore, B., Gesser, B., Dejgaard, K., Vandekerckhove, J., Human Cellular Protein Patterns and their Link to Genome DNA Sequence Data: Usefulness of Two-Dimensional Gel Electrophoresis and Microsequencing, FASEB Journal, 5, 2200-2208 (1991) (hereinafter "the Celis article") (copy annexed at Tab D);

(e) Franzen, B., Linder, S., Okuzawa, K., Kato, H., Auer, G., Nonenzymatic Extraction of Cells from Clinical Tumor Material for Analysis of Gene Expression by Two-Dimensional Polyacrylamide Gel Electrophoresis, Electrophoresis, 14, 1045-1053 (1993) (hereinafter "the Franzen article") (copy annexed at Tab E);

(f) Bjellqvist, B., Basse, B., Olsen, E., Celis, J.E., Reference Points for Comparisons of Two-Dimensional Maps of Proteins from Different Human Cell Types Defined in a pH Scale Where Isoelectric Points Correlate with Polypeptide Compositions, Electrophoresis, 15, 529-539 (1994) (hereinafter "the Bjellqvist article") (copy annexed at Tab F); and

(g) Large Scale Biology Company Info; LSB and LSP Information; from <http://www.lsbc.com> (2001) (copy annexed at Tab G).

8. Many of the published articles I considered (i.e., at least items (a)-(f) identified in paragraph 7) relate to the development of protein two-dimensional gel electrophoretic techniques for use in gene and protein expression monitoring applications in drug development and toxicology. As I will discuss below, a person skilled in the art who read the Bandman '690 application on July 14, 1997 would have

understood that application to disclose the SEQ ID NO:1 polypeptide to be useful for a number of gene and protein expression monitoring applications, e.g., in the use of two-dimensional polyacrylamide gel electrophoresis and western blot analysis of tissue samples in drug development and in toxicity testing.

9. Turning more specifically to the Bandman '690 specification, the SEQ ID NO:1 polypeptide is shown at pages 52-54 as one of three sequences under the heading "Sequence Listing." The Bandman '690 specification specifically teaches that the "invention features a substantially purified polypeptide, human integral membrane protein (NIMPH), having the amino acid shown in SEQ ID NO:1, or fragments thereof." (Bandman '690 application at page 2, lines 22-24). It further teaches that (a) the identity of the SEQ ID NO:1 polypeptide was determined from a "brain cDNA library", (b) the SEQ ID NO:1 polypeptide is the human integral membrane protein referred to as "NIMPH" and is encoded by SEQ ID NO:2, and (c) northern analysis shows that NIMPH is expressed "in various libraries, at least 46% of which are immortalized or cancerous, at least 21% involve immune response, and at least 16% involve fetal/infant tissue. Of particular note is the expression of NIMPH in neuronal (28%) and gastrointestinal (19%) tissues" and therefore NIMPH expression is "associated with cancer and neuronal and immunological disorders" (Bandman '690 application at page 13, lines 5-6, 9-10, and 20-24; and page 25, lines 8-9).

The Bandman '690 application discusses a number of uses of the SEQ ID NO:1 polypeptide in addition to its use in gene and protein expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Bandman '690 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:1 polypeptide. Consequently, my discussion in this Declaration concerning the Bandman '690 application focuses on the portions of the application that relate to the use of the SEQ ID NO:1 polypeptide in gene and protein expression monitoring applications.

10. The Bandman '690 application discloses that the polynucleotide sequences disclosed

therein, including the polynucleotides encoding the SEQ ID NO:1 polypeptide, are useful as probes in chip based technologies. It further teaches that the chip based technologies can be used “for the detection and/or quantification of nucleic acid or protein” (Bandman ‘690 application at page 23, lines 4-7).

The Bandman ‘690 application also discloses that the SEQ ID NO:1 polypeptide is useful in other protein expression detection technologies. The Bandman ‘690 application states that “[a] variety of protocols for detecting and measuring the expression of NIMPH, using either polyclonal or monoclonal antibodies specific for the protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS)” (Bandman ‘690 application at page 23, lines 13-16). Furthermore, the Bandman ‘690 application discloses that “[a] variety of protocols including ELISA, RIA, and FACS for measuring NIMPH are known in the art and provide a basis for diagnosing altered or abnormal levels of NIMPH expression. Normal or standard values for NIMPH expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to NIMPH under conditions suitable for complex formation” (Bandman ‘690 application at page 35, lines 6-10).

In addition, at the time of filing the Bandman ‘690 application, it was well known in the art that “gene” and protein expression analyses also included two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) technologies, which were developed during the 1980s, as exemplified by the Anderson 1991 and 1995 articles (Tab A and Tab B). The Anderson 1991 article teaches that a 2-D PAGE map has been used to connect and compare hundreds of 2-D gels of rat liver samples from a variety of studies including regulation of protein expression by various drugs and toxic agents (Tab A at p. 907). The Anderson 1991 article teaches an empirically-determined standard curve fitted to a series of identified proteins based upon amino acid chain length, and how that standard curve can be used in protein expression analysis (Tab A at p. 911). The Anderson 1991 article teaches that “there is a long-term need for a comprehensive database of liver proteins” (Tab A at p. 912).

The Wilkins article is one of a number of documents that were published prior to the July 14, 1997 filing date of the Bandman ‘690 application that describes the use of the 2-D PAGE technology in

a wide range of gene and protein expression monitoring applications, including monitoring and analyzing protein expression patterns in human cancer, human serum plasma proteins, and in rodent liver following exposure to toxins. In view of the Bandman '690 application, the Wilkins article, and other related pre-July 1997 publications, persons skilled in the art on July 14, 1997 clearly would have understood the Bandman '690 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 12 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in July 1997 (and for many years prior to July 1997) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identifying undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. In fact, the desire to identify and understand toxicological effects using the experimental assays described above led Dr. Leigh Anderson to found the Large Scale Biology Corporation in 1987, in order to pursue commercial development of the 2-D electrophoretic protein mapping technology he had developed. In addition, the company focused on toxicological effects on the proteome as clearly demonstrated by its goals and by its senior management credentials described in company documents (see Tab G at pp. 1, 3, and 5).

Accordingly, the teachings in the Bandman '690 application, in particular regarding use of the SEQ ID NO:1 polypeptide in differential gene and protein expression analysis (2-D PAGE maps) and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies, and

persons skilled in the art who read the Bandman '690 application on July 14, 1997 would have understood that to be so.

11. As previously discussed (*supra*, paragraphs 7 and 8), in the mid-1980s the several publications annexed to this Declaration at Tabs A through F evidence information that was available to the public regarding two-dimensional polyacrylamide gel electrophoresis technology and its uses in drug discovery and toxicology testing before the July 14, 1997 filing date of the Bandman '690 application. In particular the Celis article stated that "protein databases are expected to foster a variety of biological information... -- among others, ... drug development and testing" (See Tab D, p. 2200, second column). The Franzen article shows that 2-D PAGE maps were used to identify proteins in clinical tumor material (See Tab E). The Bandman '690 application clearly discloses that expression of NIMPH is associated with immortalized cell lines, cancerous tissue, fetal/infant tissue, neuronal tissue, gastrointestinal tissue, and with the immune response (Bandman '690 application at page 13, lines 20-24; and page 25, lines 8-9). The Bjellqvist article showed that a protein may be identified accurately by its positional coordinates, namely molecular mass and isoelectric point (See Tab F). The Bandman '690 application clearly disclosed SEQ ID NO:1 from which it would have been routine for one of skill in the art to predict both the molecular mass and the isoelectric point using algorithms well known in the art at the time of filing.

12. A person skilled in the art on July 14, 1997 who read the Bandman '690 application, would understand that application to disclose the SEQ ID NO:1 polypeptide to be highly useful in analysis of differential expression of proteins. For example, the specification of the Bandman '690 application would have led a person skilled in the art in July 1997, who was using protein expression monitoring in connection with developing new drugs for the treatment of a cancer or a neurological or immune disorder to conclude that a 2-D PAGE map that used the isolated SEQ ID NO:1 polypeptide would be a highly useful tool and to request specifically that any 2-D PAGE map that was being used for such purposes utilize the SEQ ID NO:1 polypeptide. Expressed proteins are useful for 2-D PAGE analysis in toxicology expression studies for a variety of reasons, particularly for purposes relating to

providing controls for the 2-D PAGE analysis, and for identifying sequence or post-translational variants of the expressed sequences in response to exogenous compounds. Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide sequence would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancers and neurological and immune disorders for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(b) below a number of reasons why a person skilled in the art, who read the Bandman '690 specification in July 1997, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:1 polypeptide would be a highly useful tool for analysis of a 2-D PAGE map for evaluating the efficacy and toxicity of proposed drugs for cancers and neurological and immune disorders by means of 2-D PAGE maps, as well as for other evaluations.

(a) The Bandman '690 specification contains a number of teachings that would lead persons skilled in the art on July 14, 1997 to conclude that a 2-D PAGE map that utilized the isolated SEQ ID NO:1 polypeptide would be a more useful tool for gene and protein expression monitoring applications relating to drugs for treating cancers and neurological and immune disorders than a 2-D PAGE map that did not use the SEQ ID NO:1 polypeptide. Among other things, the Bandman '690 specification teaches that (i) the identity of the SEQ ID NO:1 polypeptide was determined from a brain cDNA library, (ii) the SEQ ID NO:1 polypeptide is the integral membrane protein referred to as NIMPH, and (iii) NIMPH is expressed in various libraries derived from immortalized and cancerous tissues, neuronal and gastrointestinal tissues, and tissues involved in the immune response, and, therefore, NIMPH expression is "associated with cancer and neuronal and immunological disorders" (Bandman '690 application at page 25, lines 8-9; see paragraph 9, *supra*). The isolated SEQ ID NO:1 polypeptide could, therefore, be used as a control to more accurately gauge the expression of NIMPH in a sample, and consequently more accurately gauge the effect of a toxicant on expression of the gene.

Moreover, the Bandman '690 specification teaches that SEQ ID NO:1 shares chemical and structural homology with the integral membrane protein E25AMM from mouse. These

polypeptides share 34% identity (Bandman '690 application at page 13, lines 18-20; and Figure 2).

(b) Persons skilled in the art on July 14, 1997 would have appreciated (i) that the protein expression monitoring results obtained using a 2-D PAGE map that utilized the SEQ ID NO:1 polypeptide would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the SEQ ID NO:1 polypeptide and from the 2-D PAGE map as a whole (including all its other individual proteins). These kinds of varying results, depending on the identity of the drug being tested, in no way detract from my conclusion that persons skilled in the art on July 14, 1997, having read the Bandman '690 specification, would specifically request that any 2-D PAGE map that was being used for conducting protein expression monitoring studies on drugs for treating cancers and neurological and immune disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) utilize the SEQ ID NO:1 polypeptide. Persons skilled in the art on July 14, 1997 would have wanted their 2-D PAGE map to utilize the SEQ ID NO:1 polypeptide because a 2-D PAGE map that utilized this polypeptide (as compared to one that did not) would provide more useful results in the kind of gene and protein expression monitoring studies using 2-D PAGE maps that persons skilled in the art have been doing since well prior to July 14, 1997.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 12, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Bandman '690 application disclosing to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the SEQ ID NO:1 polypeptide.

13. Also pertinent to my considerations underlying this Declaration is the fact that the Bandman '690 disclosure regarding the uses of the SEQ ID NO:1 polypeptide for protein expression monitoring applications is not limited to the use of this protein in 2-D PAGE maps. For one thing, the Bandman '690 disclosure regarding the technique used in gene and protein expression monitoring applications is broad (Bandman '690 application at, *e.g.*, page 23, line 2 to page 24, line 4; and page 35, lines 6-14).

In addition, the Bandman '690 specification repeatedly teaches that the protein described

therein (including the SEQ ID NO:1 polypeptide) may desirably be used in any of a number of long established "standard" techniques, such as ELISA or western blot analysis, for conducting protein expression monitoring studies. See, e.g.:

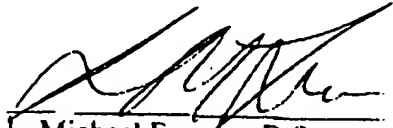
(a) Bandman '690 application at p. 23, lines 13-16 ("A variety of protocols for detecting and measuring the expression of NIMPH, using either polyclonal or monoclonal antibodies specific for the protein are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS)"); and

(b) Bandman '690 application at p. 35, lines 6-14 ("A variety of protocols including ELISA, RIA, and FACS for measuring NIMPH are known in the art and provide a basis for diagnosing altered or abnormal levels of NIMPH expression. Normal or standard values for NIMPH expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to NIMPH under conditions suitable for complex formation[.] The amount of standard complex formation may be quantified by various methods, but preferably by photometric, means. Quantities of NIMPH expressed in subject, control and disease, samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease").

Thus, a person skilled in the art on July 14, 1997, who read the Bandman '690 specification, would have routinely and readily appreciated that the SEQ ID NO:1 polypeptide, disclosed therein, would be useful to conduct gene and protein expression monitoring analyses using 2-D PAGE mapping or western blot analysis or any of the other traditional membrane-based protein expression monitoring techniques that were known and in common use many years prior to the filing of the Bandman '690 application. For example, a person skilled in the art in July 1997 would have routinely and readily appreciated that the SEQ ID NO:1 polypeptide would be a useful tool in conducting protein expression analyses, using the 2-D PAGE mapping or western analysis techniques, in furtherance of (a) the development of drugs for the treatment of cancers and neurological and immune disorders, and (b) analyses of the efficacy and toxicity of such drugs.

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14. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.


L. Michael Furness, B.Sc.

Signed at Exning, United Kingdom
this 15th day of February, 2002.